May 29, 1953

Dear Phil:

A moment's composure has finally given me a chance to review our correspondence. I'm afraid I've been rather distracted the last couple of weeks (Anderson's visit, a ms, with Cavalli flying back and forth, and another with Stocker), but things should be back to their normal pace soon.

By separate cover, I have sent 10 copies of the ms. in mimeographed form. At the time, there seemed to be no serious further issue so I did also send it off (as previously threatened) to the Journal of Immunology. I am sure no harm will come of it, as we will have an opportunity to make minor revisions when the ms. is returned by the referee, but it might have been wiser to send it back and forth for another round of critical discussion. A couple of points have come up already. I somehow overlooked your word about Miss McWhorter. Of course her part should be acknowledged, though I think putting her on as co-author on the introductory paper would be inappropriate. I will be happy to have (and follow) your advice on the details. A similar question will come up with one of my own assistants (Miss Helen Byers). I hope Miss McW will not be distressed to see the ms. in such seemingly final form-- I will be glad to ~~trade more suitably engrossed sheets, or better to~~ send another page to be inserted just before the summary.

This is not the only item I overlooked. I had intended to follow your lead on p. 9 (all references to the new copies) 4th line from bottom (substitute "known to carry a suppressed" for " suspected of carrying a covert", and on 12, 2d sentence 2d paragraph. My wording on the latter should have been confusing! The statement was wrong, and not what I meant. For the moment, it was corrected by substituting "antigenic complex" for"factor" and inserting "chemical" before substance, but I agree the sentence can be improved by more drastic revision (and it will be done).

sections which

There are two ~~points where~~ I retained against your advice, and which may need further discussion (or acquiescence). The discussion of XII_2 on p.4 is designed to repairspeculations of previous papers. On p.5, the technique of melting off the agar columns is given in such detail because I could not find it elsewhere. Anderson was glad to have the trick demonstrated to him, and like myself had made a mess of it previously. However, if I have overlooked mention either of the the use of the wire loop, or of the spinning to help break the agar, in any of your papers, I will of course withdraw the description. I am not surprised you should take this for granted aftermore than a dozen years of its practice but any novice (like myself) would be grateful for the details.

But aside from these points, I believe I have followed your remarks quite closely, though I hope you won't mind just an occasional "split verb" (cf. Fowler, Modern English Usage, pp.448 and 558, for what seems to me a moderate treatment). The latest datum on S. gallinarum had to be included (p. 9). Perhaps depending on the results of the 10[illegible] series, this paragraph may be expanded or contracted (or in view of its special interest perhaps deferred to a separate publication

However, pending your promised more complete serological analysis, I think the result should be mentioned here.

I cannot think of anything more to do with the substance of the paper.

Of course several issues have had to be scouted carefully, until we know more about them. We have a long way to go before we can say we understand S. abortus-equi. I think there is some indication, however, that monophasic strains fall into three groups:

1) Like SW-666, H-901, from which diphasics have yet to be obtained.

2) Like S.--java and derivatives, and SW959, to which an additional phase can be transduced to give a diphasic. It is by no means clear whether diphasicity here is a simple consequence of transferring an effective alternative antigen (which may be lacking in the original strain).

Attempts to get indirect evidence of an alternative phase in these stocks by experiments analogous to S. ab.-equi --x SW-666 have given entirely negative results.

3) Like S. abortus-equi (and S. paratyphi A?) in which an alternative phase can be demonstrated, albeit with great difficulty. The situation here should possibly be reviewed along the lines of the kunzendorf results. The fact that ab.-equi is fundamentally diphasic, although with an apparent very low rate indeed, is confirmed, I think by the --x SW-666 experiment. The S. abortus-equi strains I have looked at so far have all been extraordinarily sluggish in motility agar, although their H-agglutinability and microscopic motility is exemplary. This may have something to do with the phase variation results. Also, as I have already indicated, I am by no means convinced that SW-1003 was a transduction, in the sense of having anything to do with the added phage, but more experiments are needed. (Thanks for sending the 4 strains just received. Before I've had a chance to look at them, I also received a large shipment from Dr. Moran, out of which I hope I may find some more satisfactory strains.)

This group may possibly include two categories: a) in which the rate is only apparently low, owing to technical side-issues, and b) truly low rates. Would you be surprised if S. javiana turned out to the be the former, in view of the lz28:1,5 crossreaction?

Concerning the rule of one-factor-per-transduction, I am still convinced this is the rule, although I hope we will ultimately find a number of exceptions. It is based on a good deal of previous work, in which SW-666 was quite unique. It is just for this reason that it was used so extensively, but this may tend to obscure its special quality. The abortus-equi story may turn out to be relevant to this, but it is not yet clear. Certainly in all of the ~~many~~ H-antigen transductions themselves, there were no exceptions (i.e. no cases whatever of simultaneous transduction of two phases, whereas there would have been many opportunities to see this. Some of the experiments have been replicated scores of times.) However, I hope the paper lets the facts speak for themselves, rather than laying down the dogma.

Pedigree details:-- Do you have a clean copy of the summary you sent me? If not, I will have a proper table made up. Meanwhile, here are some data to fill the lacunae indicated:

SW-960B From 5594-51 (PB -:1,2) in 1,2 serum

"SW-703" A contaminant in my original culture of your #3. Please forget it.

SW-924 TM2 --x abony IV V XII i:enx

SW-925 abony --x sendai IX XII a:enx

SW-971Not 5465-52 motilized by x- TM

~~SW-987------S.-aega---x-SW-666-~~ Cf. CDC 1235- and 1535-
did I send you these twice
also 1236- and 1533-

SW-999B I still don't understand this. My records are that SW-999B was obtained from SW-999 in z6 serum, several passages, but I would almost be willing to believe that I misread 998 for -99B.

SW-998 ph2
sendai --x abortus-equi#26 You have this as IV V XII a:1,5.
(I could find only --:1,5, but the differences is explicable. It does not seem likely that the ~~V-factor(s)~~ was transduced from sendai, as such? I think it conceivable that the restoration of V might have something to do with the ability of #26 to move through the homologous "enx" serum,) ~~especially since~~ Like SW-1003 this result is a rare one from many trials which gave nothing.

SW-1036 PB #3 in b+1,2 serum

SW-1031 sendai phl --x SW-1026 (ph i)

1043G1 was renamed SW-1041, already typed. The 1043 is just the page number in my notes (by coincidence about = current SW numbers), and I haven't decided whether to give each culture in the series an SW- number. Probably will.

I don't understand why TM2 shouldn't move in 1,2 serum. ~~I'll check~~ If this doesn't work on second trial, would you send it back?

I am still confused about java and won't try to reinfect you with the same c

The a:c and b:c derivatives previously mentioned are strong evidence that the a duplication of the H_1 factors. However, abony (enx)--x SW1053 a:c gave a:enx and c:enx respectively. I strongly suspect that these may really be a:(c):enx and (a):c:enx, since the original a:c variation was very sluggish indeed. Alternatively, the enx may (incredibly) have substituted for a non-homologous a or c factor, as can be tested by further transductions. I would not be surprised if you would rather I withhold these uncertain fragments until they showed some coherence; on the other hand this is the only way I can explain such material as comes up.

I am very sorry indeed if these monsters have intruded on the routine of your lab. Now that this paper is out, it should be possible to confine shipments and queries to rather specific issues. I will do my best to simplify this situation, but suppose that part of the difficulties are your own fault for not restraining your curiosity about them, and therefore going to such detail!!!!!!!!! That's what comes of enjoying one's work. More seriously, however, I shall be very sorry if you do not tell me of any occasion when you would prefer (or find yourself unable) rather not to go into any particular problem or set of cultures for the time being. I am sorry that you do not have the facilities and assistance that your work obviously merits, and in your position I would probably be more petulant about it.

~~I think this~~

Your report on Kunsendorf seems entirely clear cut. Does it deserve formal notice (not so much for the details as for a caveat on the principle)? There is one casual experiment I will have to repeat: the loss of reactivity of SW-958c in berlin serum after brief heating (100° 10 min.) Don't count on its veracity, but would this be ~~probably~~ inconsistent with the identification of " c' " with the O somatic antigen?

If I can now review a few incidental queries, I think this ought to tidy up our communications.

1. This Iseki business: Have you seen papers? (If not, will send). Do you have the old intertransformed cultures? Of course if you want to check these for phage yourself, I'll wait to hear your result.

2. How does abortus-equi behave in absorbed "n" serum, and how is this reagent prepared?

3. Do you have paraA O forms?

4. Just read about this: do you have Roschka's typhi O 125? We could try to remotilize and verify the d:-.

Sincerely,

Joshua Lederberg

~~224~~ 5/30

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ACKNOWLEDGMENT

The assistance rendered by Miss Alma McWhorter and Miss Helen L. Byers in carrying out many of these experiments is gratefully acknowledged.

If OK, we can add this to all of the extant copies.

P.S. I forgot to add two more points:

1. I will have to send out a few copies of the present ms. (Spicer, Stocker, Zinder) but, as this will not be subject to revision in the way that the paper itself will be, I would like your specific OK first.
I don't know how you feel about pre-publication distribution, but there are lots of copies (I have about 15 left). If you think Kauffmann should have one, by all means send it. Ditto for anyone else actively working in a related area (Bruner, Peso,...).

2. It will be some time before proof comes back, but these things have a habit of creeping up suddenly. I would appreciate your early advice on how many reprints should be ordered on your account. I suppose, too, that the sooner we can finalize any minor revisions, the better.

JL

PPS. Sumer has finally cume in. I hope your airconditioning is working (we don't have any).